REMARKS

I. Restriction Requirement/Claim Status

The Patent Office has issued a further restriction requirement as follows:

Group I: Claims 74, 76-79, 81 and 88-95 drawn to a nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide analogue at least 10% as efficiently as a naturally occurring nucleotide; and

Group II: Claims 96-103 drawn to a nucleotide incorporating enzyme variant that polymerizes a polynucleotide in a template dependent manner in the presence of a biological impurity found in blood, plasma or urine.

Applicants' attorney confirms the telephonic election of Group I claims made on April 16, 2003. This election is made without traverse. Claims 96-103 are therefore cancelled without prejudice to further prosecution in one or more related continuation or divisional applications.

To expedite prosecution, claims 74, 76, 91, and 92 have been amended to clarify language and to refer to a specific embodiment of the present invention. Claims 77, 78, and 88-90 have been canceled without prejudice. New claims 104-116 have been added and find support throughout the specification (e.g., the Example at pages 57-59; at page 4, lines 8-11; at page 13, line 1 to page 14, line 14; at page 18, lines 3-7). Accordingly, no new matter has been introduced by the foregoing amendments and new claims.

After entry of the present amendment, claims 74, 76, 79, 81, 91-95, and 104-116 are now pending. The new and amended claims all read on the species that have been previously elected.

II. Information Disclosure Statement

The Office Action indicates that copies of references CJ through CR in the Information Disclosure Statement filed on December 13, 2001 are missing. The Information Disclosure Statement which is attached to the Office Action was actually filed on November 6, 2001. Copies of references CJ through CR are being provided under separate cover in a Supplemental Information Disclosure Statement filed concurrently herewith.

III. Claim Rejections

A. 35 U.S.C. § 112, Second paragraph

Claims 74, 76-79, 81 and 88-95 stand rejected under 35 U.S.C. § 112, second paragraph, on the grounds that the terms "low fidelity," "high fidelity," and "diversifying the plurality of nucleic acids" are allegedly unclear. This rejection is respectfully traversed.

In view of the cancellation of claims 77 and 78, the rejection of these claims is rendered moot.

To expedite prosecution, claim 74 has been amended to specify that the plurality of nucleic acid segments in part (c) are recombined to produce the library of nucleic acids encoding nucleotide incorporating enzyme variants. Recombination is one of the diversification methods described in the specification. Support for this amendment can be found throughout the Specification at, for example, original claim 29, and page 27, line 25 through page 36, line 6.

Accordingly, withdrawal of the rejections under 35 U.S.C. § 112, second paragraph is respectfully requested.

B. 35 U.S.C. § 112, First paragraph (written description)

Claims 74, 76-79, 81 and 88-95 stand rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is respectfully traversed in view of the pending claims.

The present invention is directed to a nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. Nucleotide incorporating enzyme variants of the present invention represent an advance over the prior art because, *inter alia*, their sequences are derived from multiple parental nucleotide incorporating enzymes (i.e., the claimed variant is encoded by a polynucleotide that comprises segments encoding all or part of either two or more members of a family of parental RNA-dependent DNA polymerases (amended claim 74), or more than two members of a family of parental nucleotide incorporating enzymes (new claim 108), or an RNA-dependent DNA polymerase and at least one parental nucleotide incorporating enzyme from another family of nucleotide

incorporating enzymes (new claim 114)). By using sequence information from "parental" nucleotide incorporating enzymes (i.e., pre-existing enzymes already possessing the ability to incorporate nucleotides into a polynucleotide), variants of the present invention are readily created that possess the function of incorporating a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. The nucleotide incorporating variants specified in the amended and new claims differ from those having randomly introduced mutations (e.g., by error prone PCR) in that the "mutations" in the claimed variants are actually corresponding sequence from a parental nucleotide incorporating enzyme. The structure of the claimed variants is thus inherently defined by the recombination process by which the claimed enzymes are initially made. That is, their sequences are a chimera of pre-existing parental nucleotide incorporating enzymes.

Applicants' invention is of the type that is difficult to expressly describe in structural terms (i.e., an enzyme that is prepared by recombining nucleotide segments encoding all or parts of other enzymes). However, the process by which the claimed variants are initially generated inherently provide such structural definition. In view of this, Applicants have claimed their invention with a set of product by process claims. The case law is clear that product by process claims are permissible even beyond the situation where the invention is not capable of precise description in structural terms. See *In re Pilkington*, 162 U.S.P.Q. 620 (CCPA 1968); *Ralston Purina Co. v. Far-Mar-Co, Inc.*, 222 U.S.P.Q. 863 (D. Kan. 1984), *aff'd in part & rev'd in part*, 227 U.S.P.Q. 177, 197 (Fed. Cir. 1985) ("A claim for a product defined by the process of making the product, or product-by–process claim, is proper and not indefinite when the product is not fairly susceptible to description by its properties or structure). Furthermore, with an invention such as that claimed by Applicants in the present application, the predecessor court to the Federal Circuit stated that "the right to a patent on an invention is not to be denied because of the limitations of the English language, and . . . may be defined by the process of making it." *In re Bridgeford*, 149 U.S.P.Q. 55, 58 (C.C.P.A. 1966).

The court in *Ralston Purina C. v. Far-Mar-Co, Inc.*, 222 U.S.P.Q. 863, 896 (D. Kansas 1984), *aff'd in part & rev'd in part*, 227 U.S.P.Q. 177 (Fed. Cir. 1985), determined whether certain product by process claims were entitled to the effective date of a prior application, and as such, determined whether the description requirement of § 112 was satisfied as to the prior application. In its conclusion of law, the court stated that:

> 43. A claim for a product defined by the process of making the product, or product-by-process claim, is proper and not indefinite when the product is not fairly

> susceptible to description by its properties or structure. Application of Pilkington, 411 F.2d 1345, 1349, 162 USPQ 145, 147-148 (CCPA 1969). Beyond this, product-by-process claims are proper even if the product is capable of description in an allowable product claim, if the product is incapable of description by product claims which are of a different scope. Application of Hughes, 496 F.2d 1216, 1219, 182 USP 106, 108 (CCPA 1974). Moreover disclosure of a process which inherently produces a compound can be adequate support for a later claiming of the product-by-process compound. Application of Edwards, supra at 1352, 196 USPQ at 467-468.
>
> * * *
>
> As was well stated by the court in Congoleum Industries, Inc. v. Armstrong, 339 F.Supp. 1036, 1055, 173 USPQ 147, 161-162 (E.D. Pa. 1972), aff'd 510 F.2d 334, 184 USPQ 769 (3rd Cir.) cert. Denied, 421 U.S 988 (1975), addressing the issue of preciseness of a disclosure's delineation of the scope of an invention:
>
> > [T]he determination of sufficiency must depend on the nature of the invention claimed. The patent statue contemplates the protection of bona fide inventions, whether or not those inventions are not always capable of descriptions in terms of exact measurements, symbols and formulas, if the claims, when read in light of the specifications, reasonably inform those skilled in the art of both the use and scope of the invention, and if the delineation is as precise as the subject matter will permit, the requirement of specificity will be satisfied.

Id. at 896.

Thus, there is no per se law that prohibits product-by-process claims which are incapable of being fairly defined by structure, from satisfying the written description requirement. Applicants recognize that actual process steps are not considered as limitations in determining patentability. However, Applicants respectfully submit that the structure of the product that is inherently produced by the process specified in the claims should be considered. Applicants respectfully wish to point out that the present claims are distinguishable from the claims held invalid in *The Regents of the University of California v. Eli Lilly and Company*, 43 USPQ2d (Fed. Cir. 1997), which were not product by process claims and which did not specify structure even inherently, as the present claims do.

The Written Description Guidelines expressly suggest that Applicants' claims satisfy the Written Description requirement in Example 10. Claim 2 of that Example is a hybridization claim which the Guidelines suggest would not meet the Written Description requirement as is (i.e., "Claim

2: An isolated DNA that hybridizes with SEQ ID NO: 10."). However, the Guidelines expressly state that the Applicant could overcome the written description rejection by substituting the claim with a product by process claim:

> **"Note: Applicant may overcome the written description rejection of the product by, for example, substituting claim 2 with a product by process claim such as the one below.**
>
> Claim 2. *The isolated DNA polynucleotide prepared according to the process of claim 1.*"

Applicants' claims are similar to hybridization claims in that structure is inferred by reference to another sequence. The Guidelines indicate that such claim (see, e.g., Example 9 of the Guidelines) would be sufficient to satisfy the Written Description requirement. In the present application, Applicants' claims not only provide structural definition inherently, i.e., as product generated by the specified process, but also by inclusion of a percent identity limitation with respect to the parental enzymes from which the claimed variants are derived. Amended independent claim 74 and new independent claims 108 and 114 all require that the parental enzymes have a pairwise identity of 77.4% or greater with respect to each other. Support for this limitation can be found in the specification at page 59, line 13.

In view of the amendments and remarks provided above, Applicants respectfully request withdrawal of the rejection of the claims made under the written description requirements of 35 U.S.C. § 112, first paragraph.

C. 35 U.S.C. § 112, First paragraph (enablement)

Claims 74, 76-79, 81 and 88-95 stand rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for a Taq DNA polymerase variant as taught by Brandis et al., allegedly does not reasonably provide enablement for any nucleotide incorporating enzyme variant that incorporates a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. This rejection is respectfully traversed in view of the pending claims.

The enablement requirement has been construed to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue

experimentation. *In re Wands*, 8 USPQ2d at 1404 (Fed. Cir. 1988); see also *United States v. Telectronics, Inc.*, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988) ("The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation."). The factors to be considered include (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.* It is not proper to conclude that a disclosure is not enabling based on an analysis of only one of the above factors while ignoring one or more of the others. MPEP at 2164.01(a).

With respect to factors (1) and (2), the disclosure is replete with specific guidance as to how to make the claimed nucleotide incorporating variants using recombination methods (Specification at page 27, line 25 through page 36, line 6; original claims 84, 85, and 86 which are supported by the Specification at page 30, line 12 to page 31, line 11) and how to screen the variants using high throughput methods to identify one having the ability to incorporate a non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide (a description of which nucleotide analogues to screen against is provided at page 20, line 13 to page 21, line 15; a prescreen to eliminate inactive polymerase variants is provided at page 46, lines 19-31; a high throughput purification method is described at page 47, lines 1-20; high throughput assay methods are provided at page 47, line 21 to page 49, line 14; a high throughput solid phase screen is provided at page 49, lines 15-27). The disclosure includes citations to many publications that report the use of recombination methods to generate variants. The screening and prescreen methods described in the specification are those which facilitate rapid identification of the claimed variant. Accordingly, Applicants' disclosure provides ample direction which minimizes the amount of experimentation required to make the claimed variant.

With respect to factor (3), the specification provides further guidance as to how to make the claimed variants in the example provided at page 57, line 22 to page 62, line 17. With respect to factors (4) and (5), the invention is directed to a nucleotide incorporating enzyme variant that can be readily made using recombination methods that are well known in the prior art and using screening methods which are well described in Applicants' disclosure.

With respect to factor (6), the use of the aforementioned recombination and screening methods to identify the claimed nucleotide incorporating enzyme variants is standard practice to those who practice in this art. It is respectfully submitted that a skilled person in the art would not consider the quantity of experimentation necessary to practice the claimed invention undue, in view of what is known in the prior art and the teaching provided in Applicants' disclosure. With respect to factor (7), "'predictability or lack therof' in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention." MPEP at § 2164.03. Applicants have described how to generate and screen the claimed variants by both citation to publications in the prior art, as well as by express disclosure in the application itself. It is well within the ability of a skilled person in the art to practice the described methods in order to readily generate the claimed variants.

With respect to factor (8), Applicants respectfully disagree with the Office Action which states that the claims are so broad as to encompass any nucleotide incorporating enzyme variant that incorporates any non-natural or rare nucleotide analogue at least about 10% as efficiently as a naturally occurring nucleotide. The claimed nucleotide incorporating enzyme variant is in fact defined by structure as explained in part B of this Amendment. The enablement requirement of the first paragraph of § 112 requires no more than a disclosure sufficient to enable one of skill in the art to practice the full scope of the claimed invention without undue experimentation. It is respectfully submitted that in view of the teaching provided in Applicants' disclosure, the state of the prior art at the time of the filing of the present application, and the skill level of the practioner in this art, that the disclosure is enabling as to the full scope of the pending claims.

The Office Action further states that Applicants' disclosure is deficient because it does not establish: (A) regions of the protein structure which may be modified without effecting nucleotide incorporation activity; (B) the general tolerance of nucleotide incorporating enzymes to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a nucleotide incorporating enzyme with an expectation of obtaining the desired biological function; and (D) sufficient guidance as to which of the essentially infinite possible choices is likely to be successfully (citing Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction (1994)). The Office Action then concludes that it would require undue experimentation

for one skilled in the art to arrive at the majority of those polypeptides of the claimed genus having the claimed nucleotide incorporation activity.

It appears from these comments that an assumption has been made that a rational scheme for introducing mutations is the only way in which variants having a desired property can be generated. This assumption is incorrect. Recombination methods, which do not rely on *a priori* knowledge of structure/function relationships, are widely recognized as having been successfully applied to generate protein variants. These methods are reported in the publications incorporated by reference throughout Applicants' disclosure (see e.g., Specification at page 27, line 25 through page 36, line 6). What matters, therefore, is not whether Applicants describe a specific, inefficient approach to generating the claimed variants, but whether Applicants' disclosure is enabling with respect to the scope of the claims. In view of the discussion above, Applicants respectfully submit that the disclosure satisfies the requirements of the enablement requirement under 35 U.S.C. § 112, first paragraph. Accordingly, withdrawal of this rejection is respectfully requested.

D. 35 U.S.C. § 102 (e)

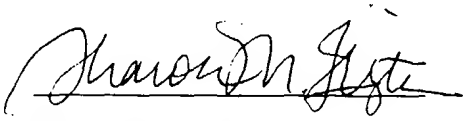
Claims 74, 76, 77-79, 81, 88-95 are rejected under 35 U.S.C. 102(e) as being anticipated by Brandis et al. (U.S. Patent No. 6,265,193). This rejection is respectfully traversed in view of the pending claims.

The Brandis et al. patent describes Taq DNA mutants that exhibit reduced discimination of fluorescein-type dye labeled nucleotides compared to naturally occurring DNA polymerase. However it does not describe, *inter alia,* the claimed features of the polynucleotide that encodes the variant, i.e., a polynucleotide that comprises segments encoding all or part of either two or more members of a family of parental RNA-dependent DNA polymerases (amended claim 74), or more than two members of a family of parental nucleotide incorporating enzymes (new claim 108), or an RNA-dependent DNA polymerase and at least one parental nucleotide incorporating enzyme from another family of nucleotide incorporating enzymes (new claim 114). Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. § 102(e).

CONCLUSION

In view of the amendments and remarks provided above, it is respectfully submitted that the pending claims are in condition for allowance and notification to that effect is respectfully requested. Should the Examiner believe that a telephone conference would expedite the prosecution of this application, the undersigned can be reached at the telephone number set forth below. The Commissioner is hereby authorized to charge any deficiency in fees or credit any overpayment to in connection with this submission to Deposit Account No. 50-0990.

October 22, 2003

By: 

Sharon M. Fujita
Attorney for Applicants
Reg. No. 38,459

MAXYGEN, INC.
Intellectual Property Department
515 Galveston Drive
Redwood City, California 94063
(650) 298-5421 (Telephone)
(650) 298-5446 (Facsimile)
Customer No. 30560